cally within an hour. She could open her eyes and she communicated and answered questions correctly by blinking. Pupillary reflex recovered and voluntary eye movements were limited only at the extreme lateral gaze. Muscle power was grade 3 and 4 in the proximal and distal parts of the four limbs. Tendon reflexes were still absent. She was taken off mechanical ventilation the next day. Her clinical condition continued to improve and her symptoms subsided in a stepwise pattern, in response to each course of haemodialysis (figure). When recalling, she could remember certain events such as the recording of the EEG, but was "too weak to move" at that time. She regained her initial strength by the time she was discharged on day 16.

When analysing the remains of the cooked fish (identified as *Yongeichthys nebulosus*), tetrodotoxin was demonstrated by thin layer chromatography, high performance liquid chromatography, and cellulose acetate membrane electrophoresis. Toxicity was assayed by using Institute of Cancer Research strain adult male mice and the toxicity score was 25 mouse units (MU)/g in fish muscle (1 MU=0.178 μg in the ICR strain mouse).[1]

Tetrodotoxin exerts its effect through binding with and blocking the voltage dependent sodium channel.[2] The voltage clamp experiments showed that tetradotoxin diminished the early sodium inward current responsible for the depolarisation of excitatory membrane. The gating properties of the sodium channel, such as the activation and inactivation mechanism, are not altered—that is, the sodium channel is not permanently damaged and its function recovers when the bound toxin is released. In uraemia, ion conductance through the sodium channel is also impaired. Sodium permeability through excitatory membranes is reduced and small inward sodium current and reduced action potential amplitudes are noted in experimental uraemic neuropathy.[3] By contrast with the effects of tetrodotoxin, uraemia changes the basic property of the sodium channel by an increased inactivation and an impaired activation mechanism. The excitability of peripheral nerves will be more significantly depressed when these two conditions combine. The synergistic effect of uraemia and tetrodotoxin is obvious in this incident in which the patient and her husband ingested roughly an equal amount of tetrodotoxin (about 200 μg, calculated from toxic score times the weight of ingested fish). The amount is about 10% of the estimated lethal dose in humans—2200 μg/60 kg body weight[4] (body weights of the patient and her husband were 54.5 and 62 kg respectively)—and caused no clinical evidence of poisoning in the healthy person. It was of interest that the CNS was relatively spared from the toxicity as the EEG showed a posterior dominant, promptly reactive alpha rhythm and the patient retained consciousness when the symptoms were at their most severe.

One of the most striking clinical features in our patient was the response to haemodialysis. Despite the small amount of toxin ingested, the dramatic improvement of her clinical condition was most likely attributed to the rapid elimination of absorbed toxin in the course of haemodialysis, rather than spontaneous recovery. The physical and chemical properties of tetrodotoxin are also supportive to this hypothesis.[5] It has a low molecular weight ($C_{11}H_{17}N_3O_8$), is water soluble, and is not significantly bound to protein—all these features are often found in toxins amenable to haemodialysis. Traditionally, the management of tetrodotoxin intoxication is mainly supportive, such as gastric lavage to remove unabsorbed toxin and machine assisted ventilation when respiration is severely affected. We suggest that haemodialysis may be an effective method in the treatment of tetrodotoxin intoxication.

MIN-YU LAN
SHUNG-LON LAI
SHUN-SHENG CHEN
Department of Neurology, Kaohsiung Medical College, Kaohsiung City, Taiwan

DENG-FWU HWANG
Department of Food Science, National Taiwan Ocean University, Keelung City, Taiwan

Correspondence to: Dr Shun-Sheng Chen, Department of Neurology, Kaohsiung Medical College Hospital, 100 Shih-Chung 1st Road, Kaohsiung City 807, Taiwan. Telephone 00886 7 3121101 ext 6771; fax 00886 7 3234237; email sheng@mail.nsysu.edu.tw

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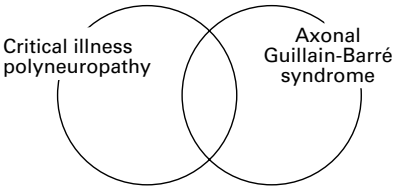
Relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome

The clinical entity critical illness polyneuropathy occurs almost exclusively in patients in critical care units and has been characterised as a complication of sepsis and multiple organ failure.[1 2] Critical illness polyneuropathy may be a common cause of the difficulty in weaning patients from the ventilator, particularly those who show intractable ventilator dependence. All the measures used to prevent or treat sepsis and multiple organ failure are the main methods now used to deal with critical illness polyneuropathy. Knowledge of this type of polyneuropathy is of help in making decisions about respirator techniques, nursing care, prognosis, and overall management. Moreover, recognition of critical illness polyneuropathy indicates the need for physiotherapy, rehabilitation, and other supportive measures as the patient recovers. Bolton *et al*[1] have made an important positive contribution to the care of patients with critical illness polyneuropathy. The actual aetiology, however, has yet to be determined. The pathogenesis needs to be clarified to treat patients more effectively.

Critical illness polyneuropathy invariably occurs at the peak of critical illness and sepsis, but in Guillain-Barré syndrome there is a brief period of recovery after a relatively minor illness or inoculation. Except for differences in the predisposing causes, as Bolton *et al*[1] reported, it is difficult to distinguish critical illness polyneuropathy from Guillain-Barré syndrome on purely clinical grounds. In both, polyneuropathy runs a monophasic course, the onset being relatively acute but with subsequent improvement in most instances. The clinical features also are similar; evidence of muscle weakness in all



four limbs, occasional involvement of facial muscles and frequent involvement of the muscles of respiration, the depression or absence of deep tendon reflexes, and some evidence of distal sensory impairment.

The first step by Bolton *et al*[1] in determining exact aetiology was to differentiate critical illness polyneuropathy from Guillain-Barré syndrome. In reviewing the patients with critical illness polyneuropathy and Guillain-Barré syndrome who were studied in their EMG laboratory, they found marked differences between the two types of polyneuropathy. Patients with Guillain-Barré syndrome had greater slowing of the speed of impulse conduction, and, in the initial stages, abnormal spontaneous activity in the muscle was absent, indicative of a predominantly demyelinating polyneuropathy. The CSF was only mildly increased in patients with critical illness polyneuropathy, but it was much increased in patients with Guillain-Barré syndrome. Comprehensive studies done at necropsy and nerve biopsies of patients with critical illness polyneuropathy showed the presence of primary axonal degeneration of the motor and sensory fibres, mainly distally, with no evidence of inflammation.[2] Zochodne *et al* (including Bolton) therefore concluded that the two types of polyneuropathies most probably are separate entities.

Guillain and colleagues enumerated the clinical and spinal fluid features of one form of acute flaccid paralysis without regard for the underlying physiology or pathology. Classic pathological studies of Guillain-Barré syndrome, however, have identified prominent demyelination and inflammatory infiltrates in the spinal roots and nerves. Guillain-Barré syndrome often has been considered to be synonymous with the pathological designation of acute inflammatory demyelinating polyneuropathy, and physiological abnormalities consistent with demyelination have been taken as supportive evidence for the diagnosis of Guillain-Barré syndrome. Feasby *et al* (with Bolton)[3] first called attention to patients who were clinically considered as having Guillain-Barré syndrome, but who were characterised electrophysiologically as having early axonal degeneration of the motor and sensory nerve fibres. The evidence included a rapid fall in compound muscle action potentials and sensory nerve action potentials, and no evidence of demyelination. Such patients often had severe paralysis and made a slow recovery, presumably reflecting the need to regenerate axons rather than remyelination. Pathological findings are consistent with axonal degeneration without demyelination. Feasby *et al*[3] termed this pattern *axonal Guillain-Barré syndrome* and suggested that there is a fundamental difference in the underlying pathophysiology, resulting in primary axonal damage rather than demyelination. Griffin *et al*[4] then confirmed the existence of the acute motor-sensory axonal neuropathy (AMSAN) pattern of Guillain-Barré syndrome described by Feasby *et al*.[3]

Infection caused by the gram negative bacterium *Campylobacter jejuni*, a leading cause

of acute diarrhoea, commonly precedes the development of Guillain-Barré syndrome.[5] There is a close association between axonal Guillain-Barré syndrome and antecedent *C jejuni* infection.[5] The antecedent infectious symptom was diarrhoea in three of five patients with axonal Guillain-Barré syndrome described by Feasby *et al*.[3] Observations by Griffin *et al*[4] confirmed that AMSAN follows *C jejuni* infection. Serum samples from patients with axonal Guillain-Barré syndrome subsequent to *C jejuni* enteritis often have IgG class autoantibodies to gangliosides GM1, GM1b, GD1a, or GalNAc-GD1a in the acute phase of the illness,[6] and there is molecular mimicry between these gangliosides and the lipopolysaccharides of *C jejuni* isolates from patients with Guillain-Barré syndrome.[6] This ganglioside mimicry may trigger high production of the IgG antiganglioside antibodies, and these autoantibodies may cause motor nerve dysfunction in patients with GBS.

Interestingly, Hagensee *et al*[7] reported a case of *"C jejuni* bacteremia and subsequent Guillain-Barré syndrome" that occurred in a patient with chronic graft versus host disease after allogenic bone marrow transplantation. Because there was acute flaccid paralysis associated with sepsis, some physicians might have diagnosed critical illness polyneuropathy. Conversely, the existence of this case strongly suggests that some diagnoses of critical illness polyneuropathy should actually be axonal Guillain-Barré syndrome or AMSAN. Our hypothesis of the nosological relation between critical illness polyneuropathy and axonal Guillain-Barré syndrome is shown in the figure. Serum IgG antibodies against GM1, GM1b, GD1a, or GalNAc-GD1a could be used as immunological markers for axonal Guillain-Barré syndrome.[6] To examine the aetiology of critical illness polyneuropathy and its nosological relation to axonal Guillain-Barré syndrome, it is necessary to investigate whether patients with critical illness polyneuropathy have antiganglioside antibodies during the acute phase of the illness.

NOBUHIRO YUKI
KOICHI HIRATA
Department of Neurology,
Dokkyo University School of Medicine, Japan

Correspondence to: Dr Nobuhiro Yuki, Department of Neurology, Dokkyo University School of Medicine, Kitakobayashi 880, Mibu, Shimotsuga, Tochigi 321–0293, Japan.

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Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia: a pilot study

Recently, a new technology known as repetitive transcranial magnetic stimulation (RTMS) has been developed.[1] In 1994, the use of magnetic stimulation in clinical psychiatry was suggested.[2] Since then, it has been used in the study or treatment of obsessive-compulsive disorder, conversion disorder, schizophrenia, and particularly, depression.[3]

Our pilot study aimed to assess the possible adverse effects of this treatment in chronic schizophrenic patients with severe negative symptoms; to evaluate if direct RTMS of the prefrontal cortex might improve negative symptoms or cognitive impairments[4] in patients with chronic schizophrenia; and thirdly, to note if RTMS might modify the deficit in prefrontal cortical activity, often referred to as hypofrontality, long established in schizophrenia,[5] specially under conditions of task activation.

Six right handed patients with chronic schizophrenia were identified at the outpatient psychiatric service of the Hospital Clínic of Barcelona. There were two men and four women (mean age 39).

Exclusion criteria included alcohol or substance abuse dependence disorder in the past 5 years, focal neurological findings, systemic neurological illness, taking cerebral metabolic activator or vasodilator medications, electroconvulsive therapy within 6 months, and significant abnormal findings on laboratory examination.

All patients were taking neuroleptic drugs, but a stable dose for at least 3 months was required. All patients were studied off benzodiazepines for at least 1 week before beginning the treatment. During the RTMS, psychotropic medications were continued at the initial dosage.

All patients were admitted to hospital. Inpatients underwent the UKU side effects scale,[6] the positive and negative syndrome scale (PANSS), and a neuropsychological battery, the day before beginning the treatment and at the end of the treatment. The UKU scale was also administered after each session.

An equivalent neuropsychological battery was used on both occasions, which consisted of the block design subtest of the Wechsler adult intelligence scale, the trail making tests A and B, the FAS verbal fluency test, and two subtests of the Wechsler memory scale (the visual memory reproduction and the verbal paired associates subtests).

A brain SPECT study was performed using a rotating dual head gamma camera, fitted with high resolution fanbeam collimators. Two ^{99m}Tc-HMPAO SPECT scans with cognitive activation, such as the Wisconsin card sorting test (WCST), were performed on each patient (24 hours before the beginning of the treatment and 24 hours after the last session).

RTMS was given with a Mag Pro magnetic stimulator, 5 days a week, during 2 weeks, at a dosage of 20 Hz for 2 seconds, once per minute for 20 minutes at 80% motor threshold. The motor threshold was determined by visualisation of finger movement. A butterfly magnetic coil was placed tangential to the orbital area, on the C_3 and C_4 EEG point.

An important finding of this study was that RTMS may be given to stable schizophrenic patients without exacerbating their psychoses. All patients tolerated the RTMS well, with minimal side effects (mild headache and tinnitus).

Table Neuropsychological tests and PANSS scores

Test		*Mean (SD)*	
Block design	Pre	49 (11.95)	NS
	Post	50 (8.69)	
Trail making test A	Pre	38.3 (9.83)	NS
	Post	42.6 (14.1)	
Trail making test B	Pre	38.3 (4.5)	NS
	Post	41 (10.03)	
Inmediate visual reproduction	Pre	50.5 (4.82)	NS
	Post	54.8 (11.2)	
Delayed visual reproduction	Pre	46.19 (8.23)	p<0.05
	Post	53.8 (12.64)	
Inmediate verbal paired associates	Pre	54 (7.46)	NS
	Post	59.5 (10.03)	
Delayed verbal paired associates	Pre	8.8 (1.1)	NS.
	Post	8.8 (1.17)	
PANSS-PG	Pre	37.67 (11.15)	NS
	Post	36.5 (11.47)	
PANSS-N	Pre	31.67 (8.26)	p<0.02
	Post	27.83 (8.47)	
PANSS-P	Pre	16.83 (7.28)	NS
	Post	15.33 /7.55)	

Pre=pretreatment; Post=post-treatment; PANSS= positive and negative syndrome scale; PG=general psychopathology scale; N=negative scale; P=positive scale.

Initial SPECT of one patient was reported to be normal, showing no evidence of hypofrontality. The remainder of the patients showed hypofrontality on the initial neuroimaging. The results after RTMS indicated no change in the hypofrontality.

Negative symptoms showed a general decrease for all patients (table). Significance ($p<0.02$) was noted on the PANSS negative symptoms subscale. These patients seemed to be more sociable than when originally seen. Nevertheless, clinical effects of the RTMS were subtle and difficult to distinguish from those derived from the supportive environment of the psychiatric ward.

With regard to the neuropsychological battery, we found a general improvement in all post-treatment scores (table), but only delayed visual memory achieved significance ($p<0.05$). This feature might be basically explained by improvement of attention, specifically of the maintenance of attention, which allows the correct function of the working memory. Thus, although there are methodological limitations regarding the power of our conclusions, it is certain that there has been an improvement in the attentional capability.

We found that all patients (except one, who was always within the normal range) diminished their number of perseverative answers and errors on WCST (items characteristically altered in schizophrenia) after the RTMS. However, significance was not achieved on any WCST scores.

Two patients who initially did not perform any categories on WCST, after the treatment, achieved one category, a possible indication of improvement of their abstract thinking. This change leads us to consider a research strategy previously reported, in which the WCST is used as a screening test for selecting schizophrenic patients. Those initially achieving low category scores would be compared to higher category scorers in an effort to identify a subgroup most likely to benefit from RTMS.

Taking into account these mild improvements together, and the lack of changes in